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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,359	04/11/2002	Zeger Debyser	522-1764	6288

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EXAMINER	
HILL, MYRON G	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,359	DEBYSER ET AL.	
	Examiner	Art Unit	
	Myron G. Hill	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62- 92* is/are pending in the application.

4a) Of the above claim(s) *62- 82, 89- 92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83- 88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group VI in paper filed November 19, 2003 is acknowledged. The traversal is a "partial" traversal and the Office is considering it as a normal traverversal. The traversal is on the ground(s) that inventions VII and VIII relate to the same inventive concept as Group VI, that the examiner has not indicated different areas of classification, and that the process claims recite all the limitations product claims. This is not found persuasive because this application is filed under § 371 and restriction is based on Lack of Unity. Prior art is used to break unity of invention in claim 1. Under PCT Rule 6, there is no special technical feature to unify the invention. Applicant has not argued that there is unity of invention in respect to claim 1. Lack of Unity does not require that the examiner cite classification because unity of invention is based on a purported special technical feature. Also, the argument that the process claims recite all of the limitations product claims is not persuasive because, as indicated above, there is no special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 62- 82 and 89- 92 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 83- 88 are under consideration in this action.

Information Disclosure Statement

The information disclosure statement filed 11 April 2002 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered. The references cited in the International Search Report were submitted with the application but no form PTO-1449 was included.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 83- 88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a product. It is not clear what the metes and bounds of the product are. Is it a gag or pol gene or region thereof from what virus? It is not clear what the structure (sequence) is. The limitation of 53-63% GC is an inherent quality of the structure (sequence) of a product, not a defining amount. The amount of GC in the replacement of all non-preferred codons is not part of the claimed product. In line 3 of claim 83, it is not clear what "retroviral gene" refers to. It appears that it is normal type, not the synthetic one. In line 4, it is not clear what is meant by "non-preferred codons when referred..." in line 4 of claim 83. It appears that the claim is trying to state that the normal retroviral gene has codons that are not

preferred for use in eukaryotic cells. Also, it is not clear what is meant by "GC dinucleotide pair". Does this mean G+C content or that only GC dinucleotides are counted in the percent? It is not clear what level is meant by the term "detectable" and what this is based on. Level of activity is not clear because it could refer to activity of the protein, not just that the level of expression is enough that there is enough tested by a certain assay. Level of activity is also not clear because it is lacks a comparative standard (level of activity compared to what?).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 83- 88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an integrase construct of SEQ ID#1, does not reasonably provide enablement for producing a detectable enzymatic activity all retroviral genes with a specific percentage of optimized codons. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re* Wands, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the

presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The invention is drawn to a product that comprises a retroviral gene that has codons optimized for expression in eukaryotic cells.

The prior art teaches that plants, bacteria, eukaryotic cells and viruses do not use the same codons to code for the same amino acids in highly expressed polypeptides. This is possible because the genetic code is degenerate and most amino acids can be coded for by different RNA triplets. The art recognizes that highly expressed proteins in certain cell types use (prefer) certain codons over others and in other organisms, the same amino acid will be coded for by a different RNA triplet. See Seed (US 5786464), Table 1, for examples of highly expressed human codons compared to virus codons. The art does not teach that there is a specific correlation between number of codons changed to preferred codons and level of activity of enzymes. To increase activity, the art teaches that only some not all codons need to be changed to preferred codons to increase expression. Seed also teaches that it is not necessary to change all the codons to preferred codons because increased expression can be accomplished even with partial replacement of non-preferred codons (column 2, lines 25- 30) and that it may be necessary to replace preferred codons to decrease expression (column 2, lines 60- 63).

The specification only teaches one gene that comprises 59% G+C (page 13, top). The specification asserts that the use modified codons would result in up to 66%

G+C in a synthetic gene and that humans have about 55- 61% G+C in highly expressed genes.

There is no evidence or guidance or direction on what amount of preferred codons result in a specific detectable level of enzymatic activity. It would be expected that each gene would need to be tested to determine the level of enzyme activity. The specification does not teach what amount of changed codons result in specific levels of activity. Also, the gag gene does not only encode enzymes, but as a polyprotein, it encodes enzymes. The structural proteins encoded by gag do not have any enzymatic activity. Since the claim requires an enzymatic function, only coding regions that encode enzymes are within the scope of the synthetic gene. See Fields Virology, pages 1775-1777 and 1782.

The claims are drawn to any retroviral gag or pol gene or a region of any retroviral gag or pol gene that comprises a certain % of G+C nucleotides and has a detectable level of enzymatic activity when expressed in eukaryotic cells.

Without the disclosure of which specific changes in codons will result in a specific increase in enzyme activity to meet the limitation of the claims, each synthetic gene must be tested to determine the expression level.

Thus, it is concluded that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims without undue experimentation.

Claims 83- 88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to a synthetic retroviral gag or pol gene.

Vas-Cath Inc. v. Mahurkar ((CAFC, 1991) 19 USPQ2d 1111), clearly states that "Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See *Vas-Cath* at page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). It is respectfully submitted that the instant specification only teaches one synthetic gene sequence that encodes an integrase protein with inherent properties of structure and function.

With the exception of SEQ ID NO:1 (nucleic acid), the skilled artisan cannot envision the detailed structure of the coding sequence that has the desired enzymatic activity. One of skill in the art can determine the percent G+C of any synthetic gene made; however, that does not indicate enzyme function. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of use. Showing that certain function equates to structure is required.

See *Fiers v. Revel*, ((CAFC, 1993) 25 USPQ 2d 1601) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,((CAFC, 1991) 18 USPQ2d 1016).

Furthermore, In *The Reagents of the University of California v. Eli Lilly* ((CAFC, 1997) 43 USPQ2d 1398), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention." It is respectfully submitted that the facts in the instant application read upon the situation in *U of C v. Lilly,* drawn to nucleic acids, because the instant specification does not recite a representative number of coding sequences in order to define what falls within the scope of the claimed genus of coding sequences to convey to the artisan that such derivatives were in Applicant's possession at the time of filing.

While it is in the skill of one practiced in the art to modify the coding sequence of a gene to use preferred codons, it is not possible to know what level of expression will be obtained from the coding sequences will be until they are made and shown to be useful. Therefore only SEQ ID NO: 1, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 83- 88 are rejected under 35 U.S.C. 102(b) as being anticipated by Seed.

Claims 1, 3, and 6- 10 of Seed disclose a retroviral gag or pol gene or a region that encodes an integrase with varying levels of codons changed to preferred codons for expression in eukaryotic cells that have expression levels increased at least 200%.

Seed is silent on enzymatic activity. Since the products have the same structure as the claimed invention and have increased expression, the products must meet the limitation of detectable enzymatic activity.

Thus, Seed clearly anticipates the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Myron G. Hill whose telephone number is 571-272-0901. The examiner can normally be reached on 9am-6pm Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Myron G. Hill
Patent Examiner
February 5, 2004

JEFFREY STUCKER
PRIMARY EXAMINER